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A METHOD OF ESTERIFYING A CARBOXYLIC ACID COMPOUND

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(57) Abstract

Method of Solution

A process for producing an ester derivative of a carboxylic acid compound characterised in that a mixture of carboxylic acid compound and a base, or a salt of a carboxylic acid compound, is treated with a compound represented by R^1-X (wherein, R^1 denotes a group forming an ester ($COOR^1$) which is hydrolysed in vivo, and X denotes a halogen atom) in the presence of a phase transfer catalyst in a solvent.

Effect

To put forward a process for conversion of a carboxylic acid compound, in particular a β-lactam antibiotic into an ester derivative.

Patent Claims

Claim 1

A process for producing an ester derivative of a carboxylic acid compound characterised in that a mixture of carboxylic acid compound and a base is treated with a compound represented by R^1-X (wherein, R^1 denotes a group forming an ester ($COOR^1$) which is hydrolysed in vivo, and X denotes a halogen atom) in the presence of a phase transfer catalyst in a solvent.

Claim 2

A process for producing an ester derivative of a carboxylic acid compound characterised in that a salt of a carboxylic acid compound is treated with a compound represented by R^1-X (wherein, R^1 denotes a group forming an ester ($COOR^1$) which is hydrolysed in vivo, and X denotes a halogen atom) in the presence of a phase transfer catalyst in a solvent.

Claim 3

A process for production in accordance with Claim 1 or 2, wherein X is a chlorine atom or bromine atom.

Claim 4

A process for production in accordance with Claim 1 or 2, wherein X is a chlorine atom.

Claim 5

A process for production in accordance with any one of Claims 1-4, wherein the carboxylic acid compound is a β-lactam antibiotic.

Claim 6

A process for production in accordance with any one of Claims 1-4, wherein the carboxylic acid compound is a penem antibiotic or carbapenem antibiotic.

Claim 7

A process for production in accordance with Claim 6, wherein the carboxylic acid compound is a carbapenem antibiotic.

Claim 8

A process for production in accordance with any one of Claims 1-4, wherein the carboxylic acid compound is (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid.

Claim 9

A process for production in accordance with any one of Claims 1-8, wherein R^1 is an acyloxyalkyl group or alkoxycarbonyl oxy alkyl group.

Claim 10

A process for production in accordance with any one of Claims 1-8, wherein R^1 is a pivaloyloxymethyl group, isopropoxy carbonyl oxy ethyl group or cyclohexyl oxycarbonyl oxy ethyl group.

Claim 11

A process for production in accordance with Claim 10, wherein R^1 is a pivaloyloxymethyl group.

Claim 12

A process for production in accordance with any one of Claims 1-11, wherein the phase transfer catalyst is a quaternary ammonium compound or quaternary phosphonium compound.

Claim 13

A process for production in accordance with any one of Claims 1-11, wherein the phase transfer catalyst is benzyltriethyl ammonium halide, tetrabutyl ammonium halide or tetrabutyl phosphonium halide.

Claim 14

A process for production of (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid

pivaloyloxymethyl ester, characterised in that a mixture of (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid and a base is treated with pivaloyloxymethyl chloride in a solvent in the presence of benzyltriethyl ammonium halide, tetrabutyl ammonium halide or tetrabutyl phosphonium halide.

Claim 15

A process for production of (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid pivaloyloxymethyl ester characterised in that (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid sodium salt is treated with pivaloyloxymethyl chloride in a solvent in the presence of benzyltriethyl ammonium halide, tetrabutyl ammonium halide or tetrabutyl phosphonium halide.

Detailed Description of the Invention

(0001)

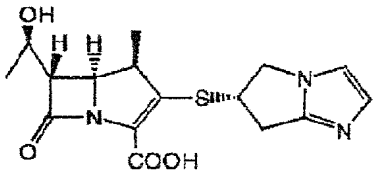
Technical Sphere of the Invention

This invention relates to a production method to convert carboxylic acid compound into ester derivative. Moreover, in particular this invention relates to a production method to convert β-lactam antibiotic into ester derivative having excellent oral absorbability.

(0002)

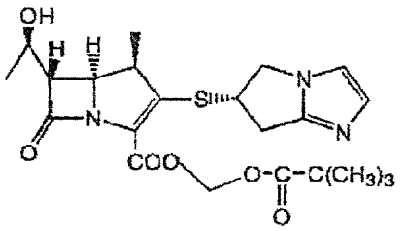
Technology of the Prior Art

(0003)



(1)

(0004)



(2)

(0005)

(1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-

hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid represented by formula (1) (Kokai 2-223587, hereinafter referred to as Compound (1)) has wide antibacterial spectrum and high antibacterial activity. On the other hand, compound represented by formula (2) (hereinafter referred to as Compound (2)) comprising esterified Compound (1) is converted into Compound (1) in vivo by oral administration and expresses antibacterial activity.

(0006)

As one process for improving the physical properties such as oral absorbability or the like, a method whereby a compound is esterified to form a prodrug is familiar to the prior art, and various kinds of esters wherein compounds are converted into prodrugs are known. As a process of esterification to derive a prodrug, a process is known wherein an iodine compound represented by R^2-I (wherein, R^2 denotes a group forming ester [$COOR^2$] which is hydrolysed in vivo) is used and treatment is carried out in the presence of base, and a process is disclosed in the Journal of the Pharmaceutical Society of Japan Vol.106, p.129 (1986) wherein a cephalosporin derivative is reacted with pivaloyloxymethyl iodide in the presence of base, and a prodrug compound esterified with a pivaloyloxymethyl group is obtained.

(0007)

Moreover, in WO96/17849, a process is described wherein a cephalosporin derivative is reacted with pivaloyloxymethyl iodide in the presence of a phase transfer catalyst (and base) to cause esterification.

(0008)

Problems to be Overcome by this Invention

However, iodine compounds represented by R^2-I, while having good reactivity, generally have the commercial drawback of poor stability. Moreover, because they are difficult to store for a long period of time, they have to be produced from chlorine compounds represented by R^2-Cl when they need to be used. Moreover, if an aforesaid Compound (1) comprising a compound having a substituent which can be quaternised, is esterified using an iodine compound represented by R^2-I, a quaternised coproduct may be produced due to quaternisation being caused together with the esterification.

(0009)

Method to Solve the Subject

Accordingly, these inventors assiduously investigated esterification methods for carboxylic acid compounds using chlorine compounds represented by R^1-Cl which are inexpensive and have excellent stability. As a result, these inventors discovered that the esterification could be achieved without using an iodine compound by causing a chlorine compound represented by

R^1-Cl to react with either a mixture of a carboxylic acid compound and base, or a salt of a carboxylic acid compound, in the presence of a phase transfer catalyst. This invention was completed on the basis of this discovery.

(0010)

Moreover, they also discovered that by reacting a chlorine compound represented by R^1-Cl, an ester derivative could be obtained without forming the quaternised coproduct even when producing an ester derivative of a compound having a substituent which can be quaternised. Moreover, with the production method of this invention, the reaction proceeds even with chlorine compounds represented by R^1-Cl which have low reactivity, and therefore moreover the reaction can be carried out even using iodine compounds represented by R^1-I and bromine compounds represented by R^1-Br having high reactivity.

(0011)

In other words, this invention relates to a process for producing an ester derivative of a carboxylic acid compound characterised in that a mixture of carboxylic acid compound and base is treated with a compound represented by R^1-X (wherein, R^1 denotes a group forming an ester [$COOR^1$] which is hydrolysed in vivo, and X denotes a halogen atom) in the presence of a phase transfer catalyst in a solvent.

(0012)

Moreover, this invention relates to a process for producing an ester derivative of a carboxylic acid compound characterised in that a salt of carboxylic acid compound is treated with a compound represented by R^1-X (wherein, R^1 denotes a group forming an ester [$COOR^1$] which is hydrolysed in vivo, and X denotes a halogen atom) in the presence of a phase transfer catalyst in a solvent.

(0013)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein X is a bromine atom or chlorine atom.

(0014)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein X is a chlorine atom.

(0015)

Moreover, this invention relates to a process for producing an ester derivative of β-lactam antibiotic wherein the carboxylic acid compound is a β-lactam antibiotic.

(0016)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein the β-lactam antibiotic is a penem antibiotic or carbapenem antibiotic.

(0017)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein the β-lactam antibiotic is a carbapenem antibiotic.

(0018)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein the carbapenem antibiotic is (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid.

(0019)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein R^1 is acyloxyalkyl group or alkoxycarbonyl oxy alkyl group.

(0020)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein R^1 is pivaloyloxymethyl, isopropoxy carbonyloxy ethyl or cyclohexyloxy carbonyloxy ethyl.

(0021)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein R1 is pivaloyloxymethyl.

(0022)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein the phase transfer catalyst is a quaternary ammonium compound or quaternary phosphonium compound.

(0023)

Moreover, this invention relates to a process for producing the aforesaid ester derivative wherein the phase transfer catalyst is benzyltriethyl ammonium halide, tetrabutyl ammonium halide or tetrabutyl phosphonium halide.

(0024)

Preferred Forms for Carrying out the Invention

Hereinafter this invention will be described in greater detail.

(0025)

This invention is a process to obtain an ester derivative of a carboxylic acid compound by reacting either a mixture of carboxylic acid compound and base, or a salt of carboxylic acid compound, with a compound represented by R^1-X in the presence of a phase transfer catalyst in a solvent.

(0026)

This invention is characterized by reacting a compound represented by R^1-X in the presence of a phase transfer catalyst, and a carboxylic acid compound or salt thereof is used as the reaction raw material. Moreover, if a carboxylic acid compound is used as the starting material, a base is caused to be copresent and the reaction carried out, but base does not need to be used if a salt of a carboxylic acid compound is used as the raw material.

(0027)

Moreover, in this specification, the term "mixture" in "mixture of carboxylic acid compound and base" means that a carboxylic acid compound and a base are both present in the treatment with the compound represented by R^1-X, but does not mean that the carboxylic acid compound and base are first reacted; however there is no restriction to the treatment procedures.

(0028)

As the solvent used in the process of this invention, amides such as dimethylformamide, dimethylacetamide and the like, dialkyl sulfoxides such as dimethylsulfoxide or the like may be proposed.

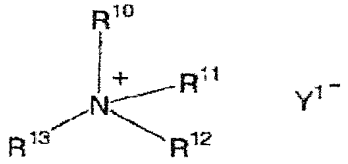
(0029)

As the phase transfer catalyst used in the process of this invention, the said catalyst may be one usually used as a phase transfer catalyst, and for example quaternary ammonium compounds, quaternary phosphonium compounds and tertiary sulfonium compounds may be proposed, but crown ether compounds may also be used.

(0030)

Such quaternary ammonium compounds are compounds represented by the following general formula.

(0031)



(wherein, R^{10}, R^{11}, R^{12} and R^{13} each independently denote an alkyl group, aryl group or aralkyl group, and Y^1 denotes a halogen atom or OH).

(0032)

As quaternary ammonium compound, a halogenated quaternary ammonium wherein Y^1 is halogen atom is preferred.

(0033)

As examples of halogenated quaternary ammonium compounds, benzyltriethyl ammonium halides, benzyl trimethyl ammonium halides, hexadecyl trimethylammonium halides, tetrabutyl ammonium halidess, trioctylmethyl ammonium halide and the like may be proposed, and benzyltriethyl ammonium halide or tetrabutyl ammonium halide is preferred.

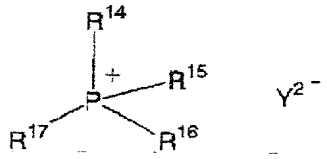
(0034)

Moreover, as halogen atom (or halide), chlorine atom, bromine atom, iodine atom and the like may be proposed, but a chlorine atom or bromine atom is preferred.

(0035)

Such quaternary phosphonium compounds are compounds represented by following general formula.

(0036)



(wherein, R^{14}, R^{15}, R^{16} and R^{17} each independently denote an alkyl group, aryl group or aralkyl group, and Y^2 denotes a halogen atom or OH).

(0037)

As quaternary phosphonium compound, a halogenated quaternary phosphonium wherein Y^2 is halogen atom is preferred.

(0038)

As examples of halogenated quaternay phosphonium compounds, tetra n-butyl phosphonium halide, tetraphenyl phosphonium halide, triphenylmethyl phosphonium halide, hexadecyl tributyl phosphonium halide and the like may be proposed, and tetra n-butyl phosphonium halide is preferred.

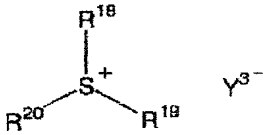
(0039)

Moreover, as halogen atom (or halide), chlorine atom, bromine atom, iodine atom and the like may be proposed, but chlorine atom or bromine atom is preferred.

(0040)

Such tertiary sulfonium compounds are compounds represented by following general formula.

(0041)



(wherein, R^{18}, R^{19} and R^{20} each independently denote an alkyl group, aryl group or aralkyl group, and Y^3 denotes a halogen atom or OH).

(0042)

As examples of tertiary sulfonium compound, a halogenated tertiary sulphonium compound wherein Y^3 is halogen atom is preferred.

(0043)

As examples of halogenated tertiary sulphonium compound, dimethyl phenyl sulphonium chloride and the like may be proposed.

(0044)

As far as crown ether compounds are concerned, dicyclohexyl-18-crown-6, 18-crown-6, dibenzo-18-crown-6 or the like may be proposed.

(0045)

As phase transfer catalysts used in this production method, quaternary ammonium compounds or quaternary phosphonium compounds are preferred.

(0046)

The quantity of phase transfer catalyst used is in a range of 0.5-5 equivalents with respect to

carboxylic acid compound, and preferably 1-1.5 equivalents.

(0047)

As the base used in this invention, the said base may be one usually used in organic chemical reaction, and for example an inorganic base such as a carbonate or hydrogencarbonate of an alkali metal such as sodium carbonate, sodium bicarbonate, potassium carbonate, lithium carbonate and the like, and an organic base such as triethylamine, diisopropyl ethylamine and the like may be nominated.

(0048)

The quantity of base used may be about an equivalent amount with respect to carboxylic acid compound.

(0049)

The reaction temperature is usually in a range of 0-70°C, and preferably from room temperature to 60°C.

(0050)

The reaction time may usually be in a range of 3-48 hours but the said time will vary corresponding to the reaction temperature, namely the reaction time may be short if the reaction temperature is high.

(0051)

When the carboxylic acid compound has a substituent having a higher reactivity than the carboxyl group, the said substituent may be protected with a protecting group or the said substituent moiety may be synthesized after the esterification which is performed beforehand.

(0052)

Group forming an ester which is hydrolysed in vivo denotes a group which may form an ester with the carboxyl group of carboxylic acid compound, and the said ester is readily hydrolysed in the human body and converted to carboxylic acid. As examples, acyloxyalkyl groups, alkoxycarbonyloxyalkyl groups, dialkylaminoalkyl groups, 2-(alkoxycarbonyl)-2-alkenyl group, lactone groups and the like may be proposed.

(0053)

As acyloxyalkyl groups, acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexyl carbonyloxy) prop-1-yl and (1-aminoethyl) carbonyloxymethyl may be proposed.

(0054)

As alkoxycarbonyloxyalkyl groups, ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl, propoxycarbonyloxyethyl, isopropoxycarbonyloxyethyl, cyclohexyloxycarbonyloxyethyl ester and the like may be proposed.

(0055)

As far as dialkylaminoalkyl groups are concerned, dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl, diethylaminoethyl and the like may be proposed.

(0056)

As far as 2-(alkoxycarbonyl)-2-alkenyl groups are concerned, 2-(isobutoxycarbonyl) pent-2-enyl, 2-(ethoxycarbonyl) but-2-enyl and the like may be proposed.

(0057)

As far as lactone groups are concerned, phthalidyl and dimethoxy phthalidyl may be proposed.

(0058)

As R^1, acyloxyalkyl group or alkoxycarbonyloxyalkyl group is preferred.

(0059)

Carboxylic acid compound denotes a compound generally having a carboxyl group, and a salt of a carboxylic acid compound denotes a compound wherein the hydrogen atom of carboxyl group is replaced by a metal atom.

(0060)

Salt of carboxylic acid compound used in this specification denotes an alkali metal salt such as sodium salt, lithium salt, potassium salt or the like or alkaline earth metal salt such as magnesium salt, calcium salt or the like.

(0061)

As β-lactam antibiotic, carbapenem derivative, penem derivative, cephalosporin derivative, penicillin derivative and the like may be proposed.

(0062)

Below this invention will be described in greater detail by reference to Examples, but it should be understood however, that this invention is not restricted to these Examples.

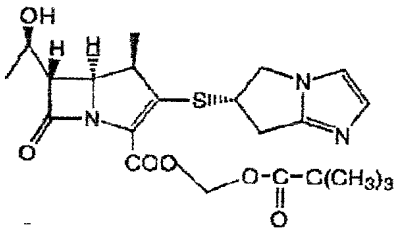
(0063)

Examples

Example 1

(1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid pivaloyloxymethyl ester.

(0064)



(0065)

1). Dimethylformamide 3.5 ml was added to (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid 350 mg, and triethylamine 131 mg, benzyltriethylammonium chloride 228 mg and pivaloyl oxymethyl chloride 166 mg were added, and the mixture was reacted at room temperature for 24 hours. Ethyl acetate was added to the reaction liquid and the liquid washed with water, dried with sodium sulfate and concentrated, and thereafter the residue was washed with ethanol, and the title compound 265 mg was obtained.

(0066)

^{1}H-NMR (DMSO-d_6) δ : 1.10 (9H, s), 1.15 (3H, d, J = 5.9 Hz), 1.21 (3H, d, J = 7.3 Hz), 2.66 (1H, dd, J = 4.4, 16.6 Hz), 3.25-3.40 (2H, m), 3.53 (1H, dt, J = 6.8, 17.1 Hz), 3.90 (1H, dd, J = 3.4, 11.2 Hz), 3.95-4.05 (1H, m), 4.25 (1H, dd, J = 2.4, 9.3 Hz), 4.46 (1H, dd, J = 6.4, 11.2 Hz), 4.5-4.6 (1H, m), 5.11 (1H, d, J = 4.9 Hz -OH), 5.70 (1H, d, J = 5.9 Hz), 5.87 (1H, d, J = 5.9 Hz), 6.92 (1H, d, J = 1 Hz), 7.06 (1H, d, J = 1 Hz).

(0067)

2). Dimethylformamide 220 ml was added to (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid sodium salt 22.2 g, and benzyltriethylammonium chloride 13.6 g and pivaloyl oxymethyl chloride 9.5 g were added, and the mixture was reacted at room temperature for 16 hours and furthermore at 30°C for five hours. Ethyl acetate was added to the reaction liquid and the liquid was washed with water, dried with magnesium sulphate, and, after concentration, the residue was washed with ethanol, and the title compound 16.4 g was obtained.

(0068)

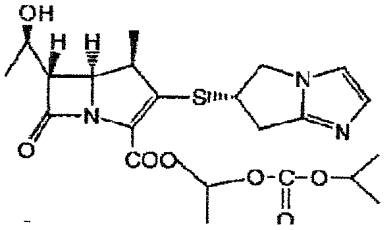
3). Dimethylformamide 3.0 ml was added to (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid 350 mg, and triethylamine 131 mg, tetra n-butyl phosphonium bromide 340 mg and pivaloyl oxymethyl chloride 166 mg were added, and the mixture was reacted at room temperature for 19 hours. Ethyl acetate was added to the reaction liquid and the liquid was washed with water, dried with sodium sulfate, and, after concentration, the residue was washed with ethanol, and the title compound 262 mg was obtained.

(0069)

Example 2

(1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid 1-(isopropoxycarbonyloxy) ethyl ester.

(0070)



(0071)

Dimethylformamide 2 ml was added to (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid sodium salt 223 mg, and benzyltriethylammonium chloride 137 mg and 1-chloroethyl isopropyl carbonate 110 mg were added, and the mixture was reacted at room temperature for 16 hours and furthermore at 55°C for seven hours. Ethyl acetate was added to the reaction liquid and the liquid was washed with water, dried with sodium sulfate, and, after concentration, purified by silica gel column chromatography, and the title compound 75 mg was obtained.

(0072)

^{1}H-NMR (DMSO) δ : 1.14-1.21 (12H, m), 1.44 (1.5H, d, J = 5.4 Hz), 1.45 (1.5H, d, J = 5.4 Hz), 2.69 (0.5H, dd, J = 5.1, 16.8 Hz), 2.71 (0.5H, dd, J = 5.1, 16.8 Hz), 3.11 (1H, m), 3.54 (1H, m), 3.90-4.00 (2H, m), 4.23 (0.5H, dd, J = 2.9, 9.3 Hz), 4.25 (0.5H, dd, J = 2.9, 9.3 Hz), 4.49 (1H, dd, J = 6.8, 11.2 Hz), 4.57 (1H, m), 4.75 (1H, m), 5.09 (0.5H, d, J = 4.4Hz, -OH), 5.10 (0.5H, d, J = 4.4Hz, -OH), 6.68 (1H, q, J = 5.4 Hz), 6.93 (1H, s), 7.08 (1H, s)

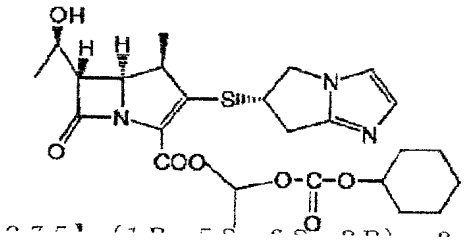
H-6 is hidden in H_2O in DMSO-d_6.

(0073)

Example 3

(1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid 1-(cyclohexyloxycarbonyloxy) ethyl ester.

(0074)



(0075)

Dimethylformamide 2 ml was added to (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid sodium salt 223 mg, and benzyltriethylammonium chloride 137 mg and 1-chloroethyl cyclohexyl carbonate 136 mg were added, and the mixture was reacted at room temperature for 16 hours and furthermore at 55°C for seven hours. Ethyl acetate was added to the reaction liquid and was washed with water, dried with sodium sulfate and was concentrated, and thereafter it was purified by silica gel column chromatography, and the title compound 102 mg was obtained.

(0076)

^{1}H-NMR (DMSO) δ : 1.14 (3H, d, J = 5.4 Hz), 1.14-1.46 (12H, m), 1.62 (2H, m), 1.80 (2H, m), 2.68 (1H, m), 3.53 (1H, m), 3.89-4.01 (2H, m), 4.24 (1H, m), 4.46-4.56 (3H, m), 5.08 (0.5H, d, J = 4.9 Hz), 5.09 (0.5H, d, J = 4.9 Hz), 6.69 (1H, q, J = 5.4 Hz), 6.90 (1H, d, J = 1.0 Hz), 7.06 (1H, d, J = 1.0 Hz)

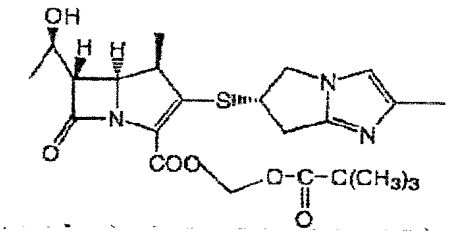
H-6, H-7'b are to be hidden in H_2O in DMSO-d6.

(0077)

Example 4

(1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-2-methyl-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid pivaloyloxymethyl ester.

(0078)



(0079)

1). Dimethylformamide 1 ml was added to (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-2-methyl-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid potassium salt 49.3 mg, and benzyltriethylammonium chloride 28 mg and pivaloyl oxymethyl chloride 29 mg were added, and the mixture was reacted at room temperature for 4 hours. Ethyl acetate was added to the reaction liquid and the liquid was washed with water, dried with sodium sulfate, and concentrated, and thereafter the residue was washed with ethanol, and the title compound 36 mg was obtained.

(0080)

^{1}H-NMR (DMSO-d_6) δ : 1.09 (9H, s), 1.15 (3H, d, J = 5.9 Hz), 1.20 (3H, d, J = 6.8 Hz), 2.07 (3H, s), 2.61 (1H, dd, J = 3.9, 17.9 Hz), 3.25-3.35 (2H, m), 3.51 (1H, m), 3.83 (1H, dd, J = 2.9, 11.2 Hz), 3.98 (1H, m), 4.24 (1H, dd, J = 2.4, 9.3 Hz), 4.38 (1H, dd, J = 6.4, 11.2 Hz), 4.45-4.55 (1H, m), 5.13 (1H, d, J = 4.9Hz -OH), 5.70 (1H, d, J = 5.9 Hz), 5.86 (1H, d, J = 5.9 Hz), 6.76 (1H, s).

(0081)

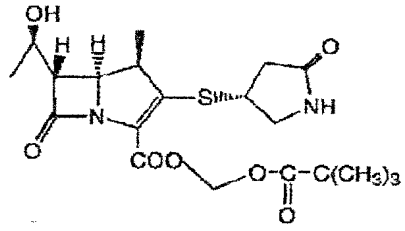
2). Dimethylformamide 1 ml was added to (1R, 5S, 6S, 8R)-2-[(6S)-6,7-dihydro-2-methyl-5H-pyrrolo[1,2-a]imidazol-6-yl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid potassium salt 49.2 mg, and tetrabutyl ammonium bromide 59.3 mg and pivaloyl oxymethyl chloride 28 mg were added, and the mixture was reacted at room temperature for three hours 30 minutes. Ethyl acetate was added to the reaction liquid and the liquid was washed with water, dried with sodium sulfate, and concentrated, and thereafter the residue was washed with ether, and the title compound 36 mg was obtained.

(0082)

Example 5

(1R, 5S, 6S, 8R)-2-[(4R)-2-oxo-4-pyrrolidinyl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid pivaloyloxymethyl ester.

(0083)



(0084)

Dimethylformamide 10 ml was added to (1R, 5S, 6S, 8R)-2-[(4R)-2-oxo-4-pyrrolidinyl] thio-6-(1-hydroxyethyl)-1-methyl-1-carbadethiapen-2-em-3-carboxylic acid 1 g, and benzyltriethylammonium chloride 654 mg and pivaloyloxymethyl chloride 476 mg were added, and the mixture was reacted at room temperature for 17 hours and furthermore at 40°C for five hours. Ethyl acetate was added to the reaction liquid and the liquid was washed with water, dried with magnesium sulphate, and, after concentration, purified by silica gel column chromatography, and the title compound 797 mg was obtained.

(0085)

^{1}H-NMR ($CDCl_3$) δ : 1.22 (9H, s), 1.28 (3H, d, J = 7.3 Hz), 1.35 (3H, d, J = 5.9 Hz), 2.11 (1H, dd, J = 5.4, 17.1 Hz), 2.81 (1H, dd, J = 7.8, 17.1 Hz), 3.26 (1H, dd, J = 2.9, 6.8 Hz), 3.29 (1H, m), 3.34 (1H, dd, J = 5.4, 10.6 Hz), 3.83 (1H, dd, J = 7.8, 10.6 Hz), 4.03 (1H, m), 4.25 (2H, m), 5.84 (1H, d, J = 5.9 Hz), 5.97 (1H, d, J = 5.9 Hz)

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